BAŞKENT UNIVERSITY

1993

25 Years

sourcing and spreading science

MANAGEMENT OF HIGH-RISK ENDOMETRIAL CANCER: ROLE OF CHEMOTHERAPY

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The 4th MEMAGO Annual Congress

in Association with the 1st Emirates

Gynecological Oncology Conference

11 Oct 2019 Abu Dhabi

Learning Objectives

- To learn the most up-to-date adjuvant chemotherapy options for operable high grade endometrial cancer
- To learn about how new trials change our pratice

High-Risk Endometrial Cancer

- Very heterogeneous group of tumors:
  - Early stage EC with high-risk features
  - Advanced stages EC
  - Non-endometrioid tumors

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

Q1: What is the current best definition of risk groups for adjuvant therapy (low risk versus (high) intermediate versus high risk)?

		LOE
Low	• Stage I Endometrioid + gr 1-2 + <50% myometrial invasion + LVSI neg	1
Low Inter	• Stage I Endometrioid + gr 1-2 + ≥50% myometrial invasion + LVSI neg	1
High Inter Risk	• Stage I Endometrioid + gr 3 + <50% myometrial invasion, regardless of LVSI status	1
	• Stage I Endometrioid + gr 1-2 + LVSI unequivocal positive, regardless of depth of invasion	2
High Risk	• Stage I Endometrioid + gr 3 + ≥50% myometrial invasion, regardless of LVSI status	1
	• Stage II & stage III no residual disease	1
	• Non endometrioid (serous or clear cell or undifferentiated carcinoma, carcinosarcoma)	1
Adv M+	• Stage III residual disease & IVa	1
	• Stage IVB	1

FIGO 2009 staging used
Molecular factors were considered but not included
Tumor size was considered but not included
Nodal status may be considered for treatment recommendations

ESMO-ESGO-ESTRO Concensus Conference Working Group. Ann Oncol 2016

5 yrs Survival
(*Old Classification*)

- **Higher incidence rates of distant metastases and death reported for HREC**

Stage / Grade	IA	IB	IC
G1	93%	92%	91%
G2	91%	93%	86%
G3	80%	82%	75%

Low risk
Intermediate risk
High risk

***+stage II,III-IV, clear cell and serous histology**

Creasman WT. IJGO, 2006

Treatment Modalities
Chemotherapy Compared with Radiotherapy Alone

- **EBRT has been standart adjuvant treatment for HREC for many decades, although there is a paucity of evidence on improvement of survival**
- **Randomised trials have compared adjuvant CT alone with pelvic EBRT alone:**
  - **Japanese trial**
  - **Italian trial**
  - **GOG-122 trial**
  - **GOG-249 trial (BRT included)**

1. *Susumu N. Gynecol Oncol 2008*
2. *Maggi R. BJC 2006*
3. *Randall ME. JCO 2006*
4. *McMeekin DS. JCO 2019*

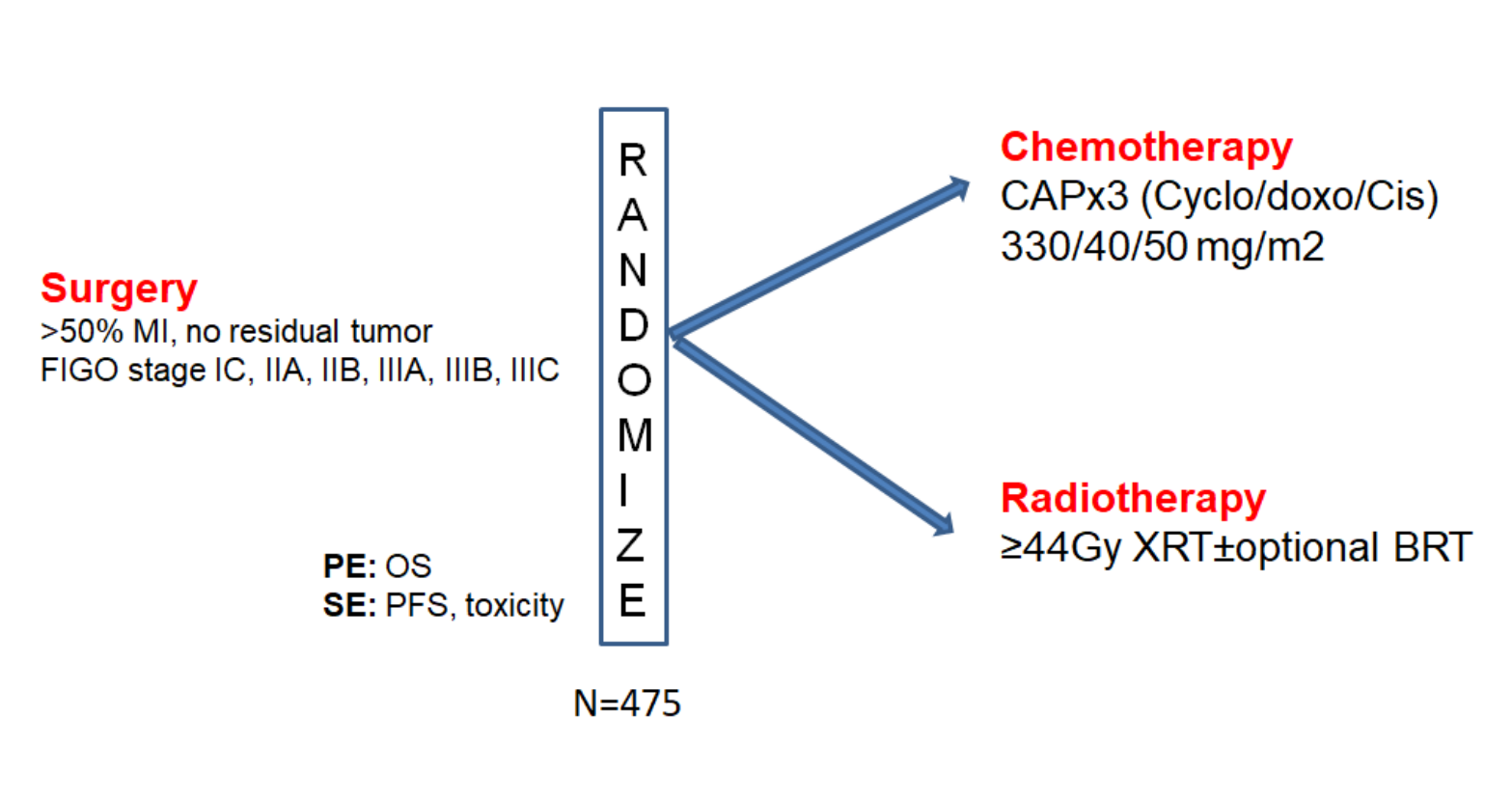
Treatment Modalities

Chemotherapy Compared with Radiotherapy Alone

	GOG 122[1]	Italian Study[2]	JGOG 2033[3]	GOG 249[4]
Population (Stage)	III-IV	IC (26%) II (8%) III (64%)	IC (61%; 55% grade 1) IIA (13%) III (24%)	IB G1 & G2 (50%) IB G3; II (50%)
n	396	345	385	601
Regimen	WART A^{60} P^{50} x 8	RT C^{600} A^{45} P^{50} x 5	RT C^{333} A^{40} P^{50} x 3	RT TC x3
PFS	Significant	-	NS	NS
OS	Significant	NS	NS	NS

1. *Randall ME. JCO 2006*
2. *Maggi R. BJC 2006*
3. *Susumu N. Gynecol Oncol 2008*
4. *McMeekin DS. JCO 2019*

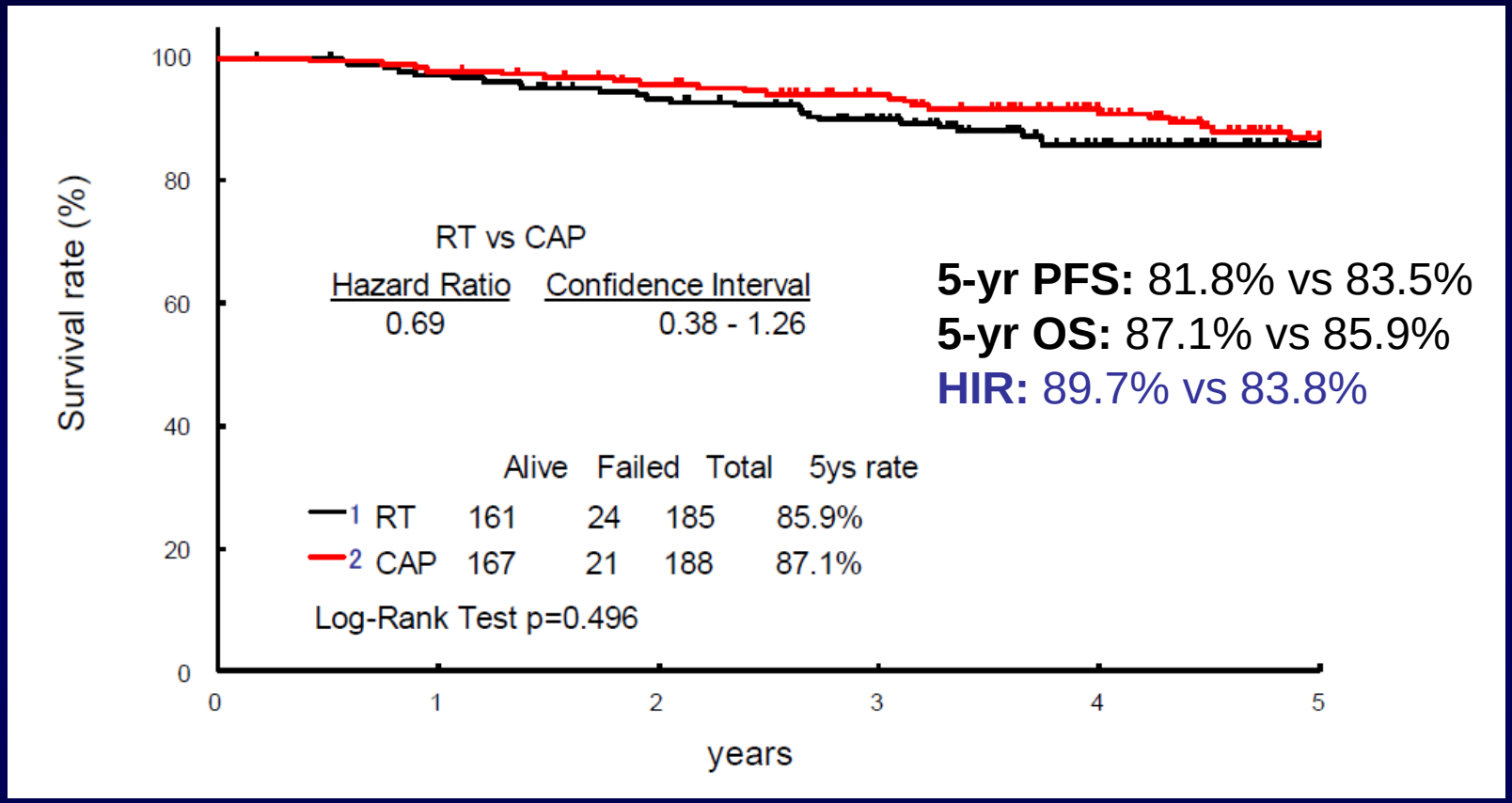
JGOG 2033



- **No significant differences in PFS and OS were observed**
- **5 yrs OS rates were good in both arms:**
  - **60% of pts had stage IC**
  - **85% grade 1-2 tumors**

Susumu N. Gynecol Oncol 2008

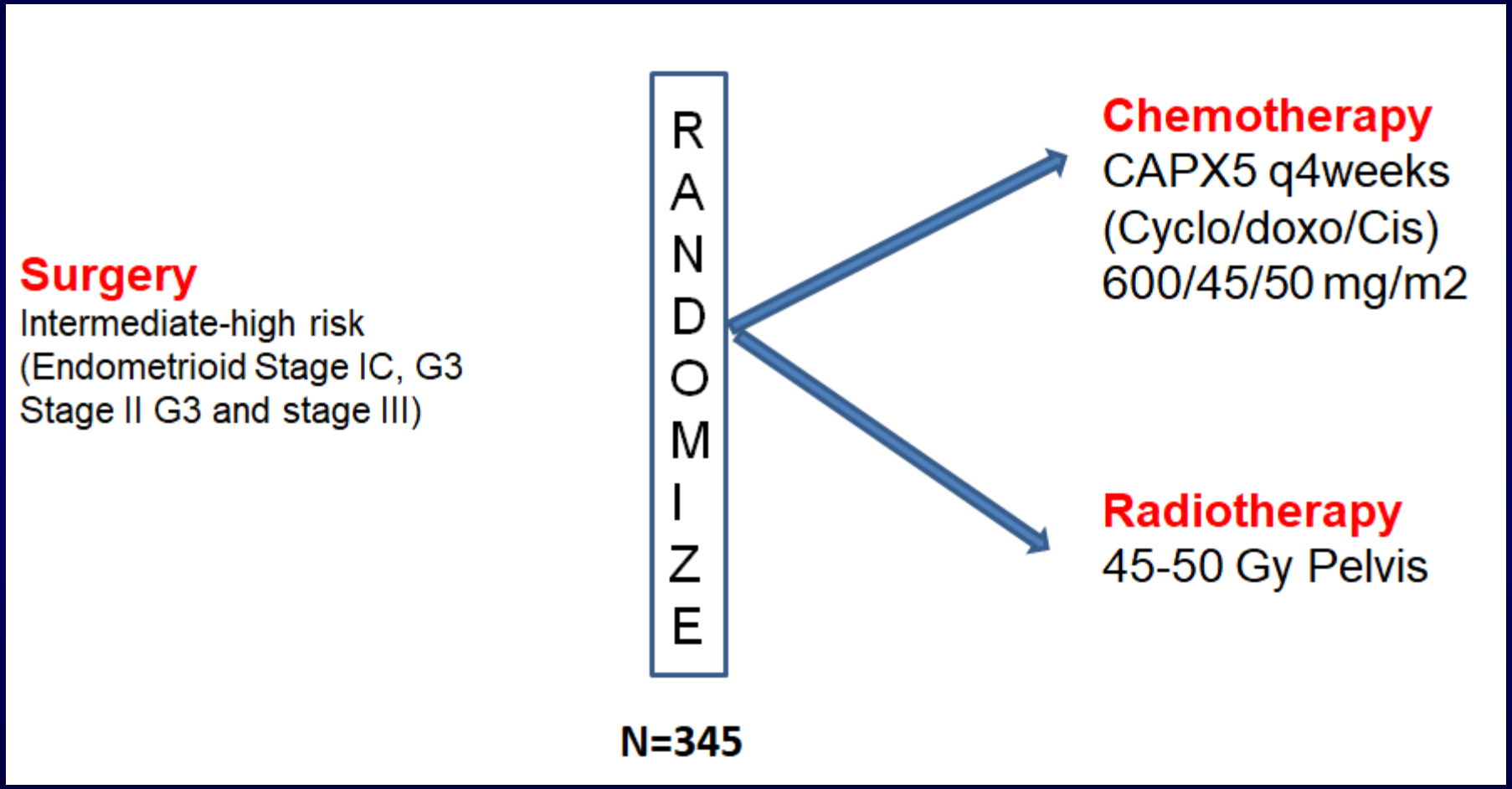
JGOG 2033-OS



- **Unplanned Subgroup Analysis:** **Pts with high risk factors (n=120) (stage IC, pts with >70 or grade 3 endometrioid or stage II/IIIA (positive cytology), might have benefit from chemotherapy, but it was not found for stage III disease**

Susumu N. Gynecol Oncol 2008

Italian Trial

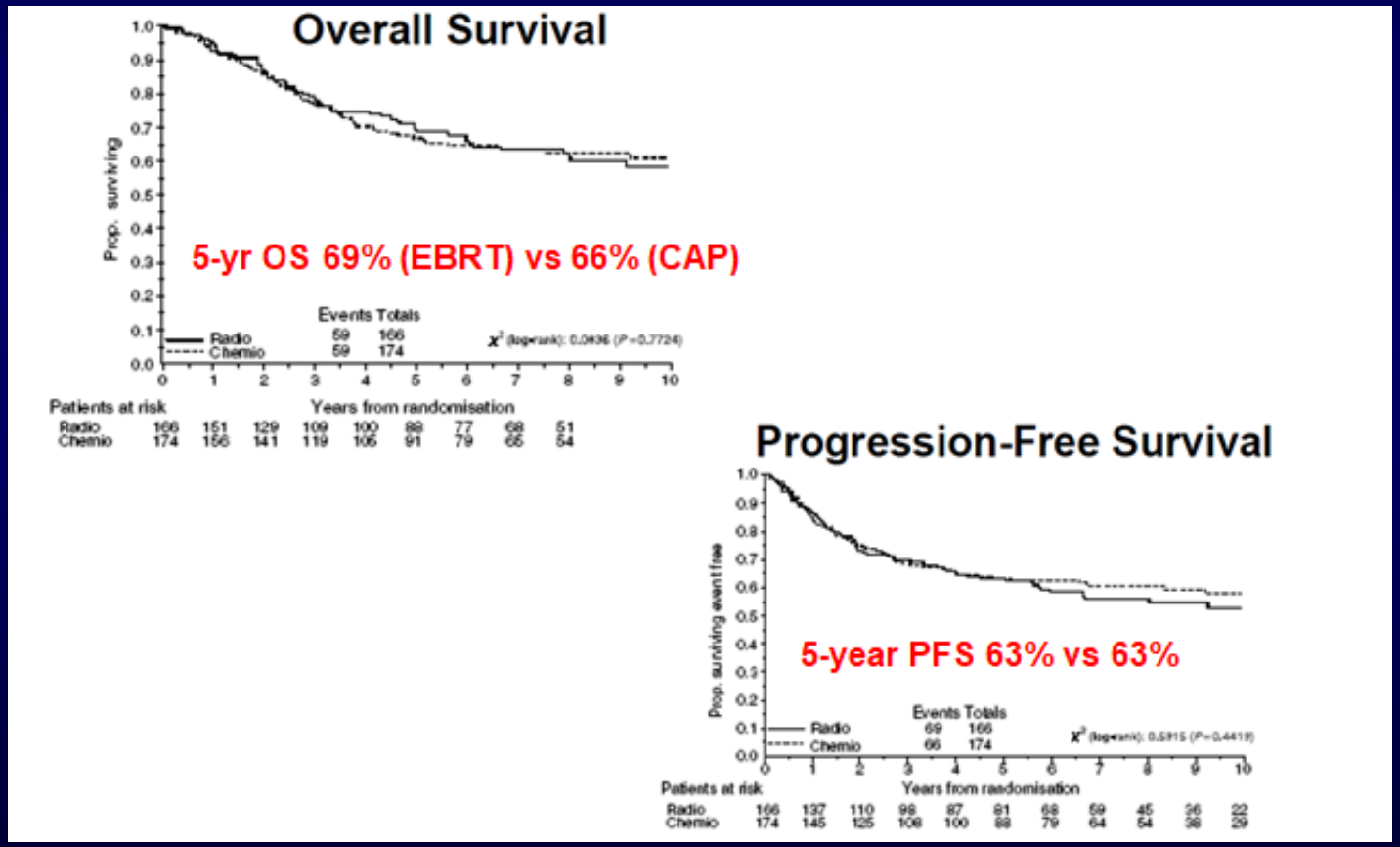


- **64% pts had grade III**
- **26% pts had grade IC**

Maggi R. BJC 2006

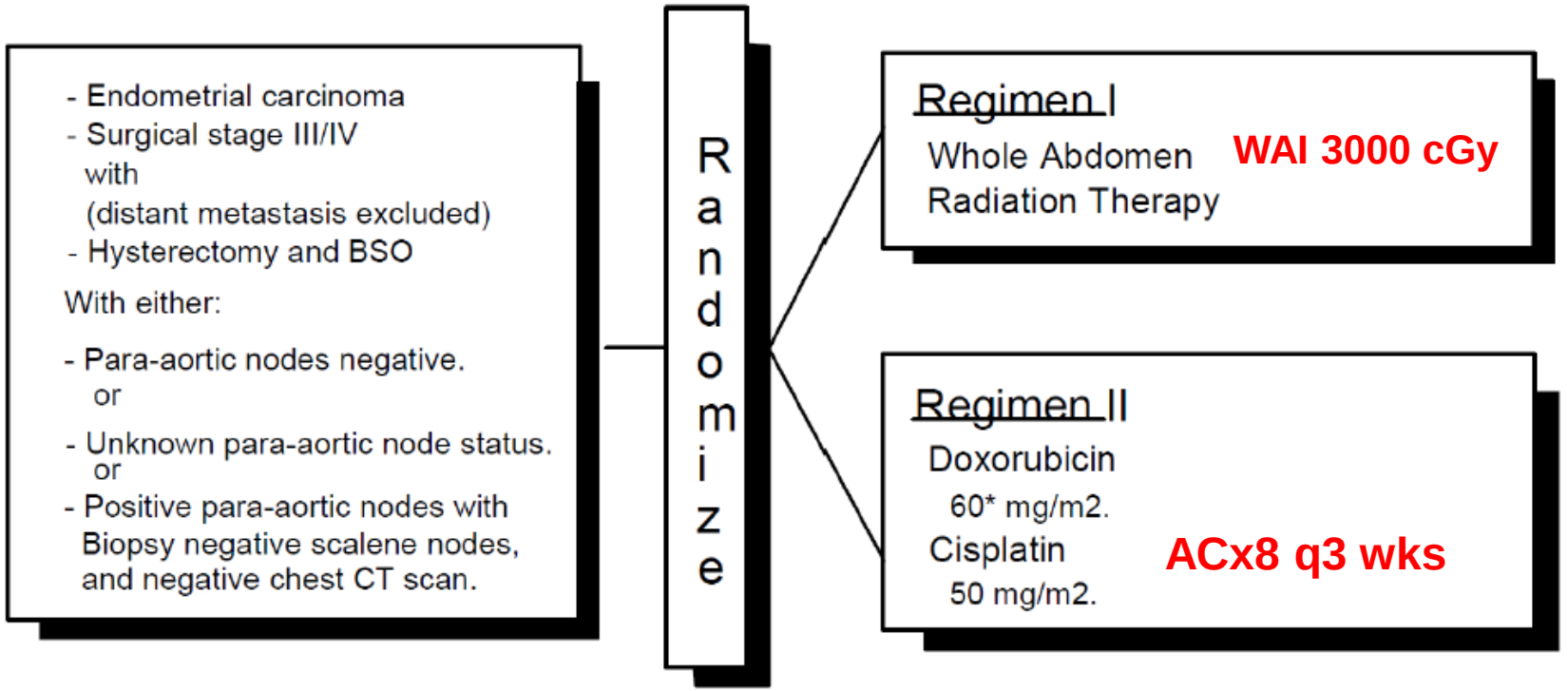
Italian Trial

- EBRT delayed pelvic recurrence and chemotherapy delayed distant mets
- No differences in OS&PFS



Maggi R. BJC 2006

GOG-122 Trial



Residual macroscopic disease <2 cm allowed

Randall ME. JCO 2006

GOG-122/OS

- CT significantly improved OS (55% vs 42%)
- 5-year rates of pelvic recurrence were 18% for CT and 13% for RT
- Substantial grade 3-4 toxicity occurred in patients treated with CT

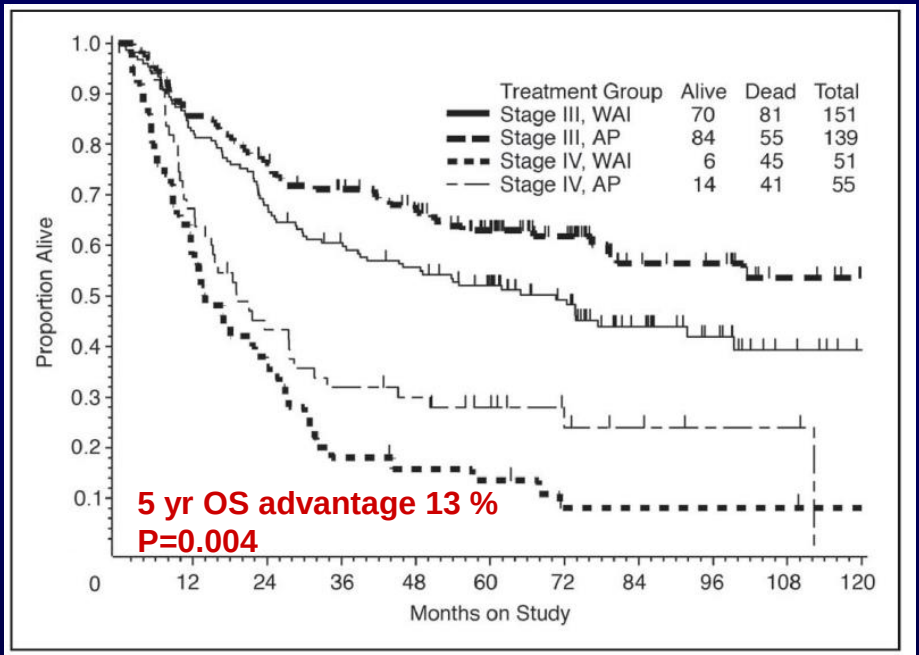


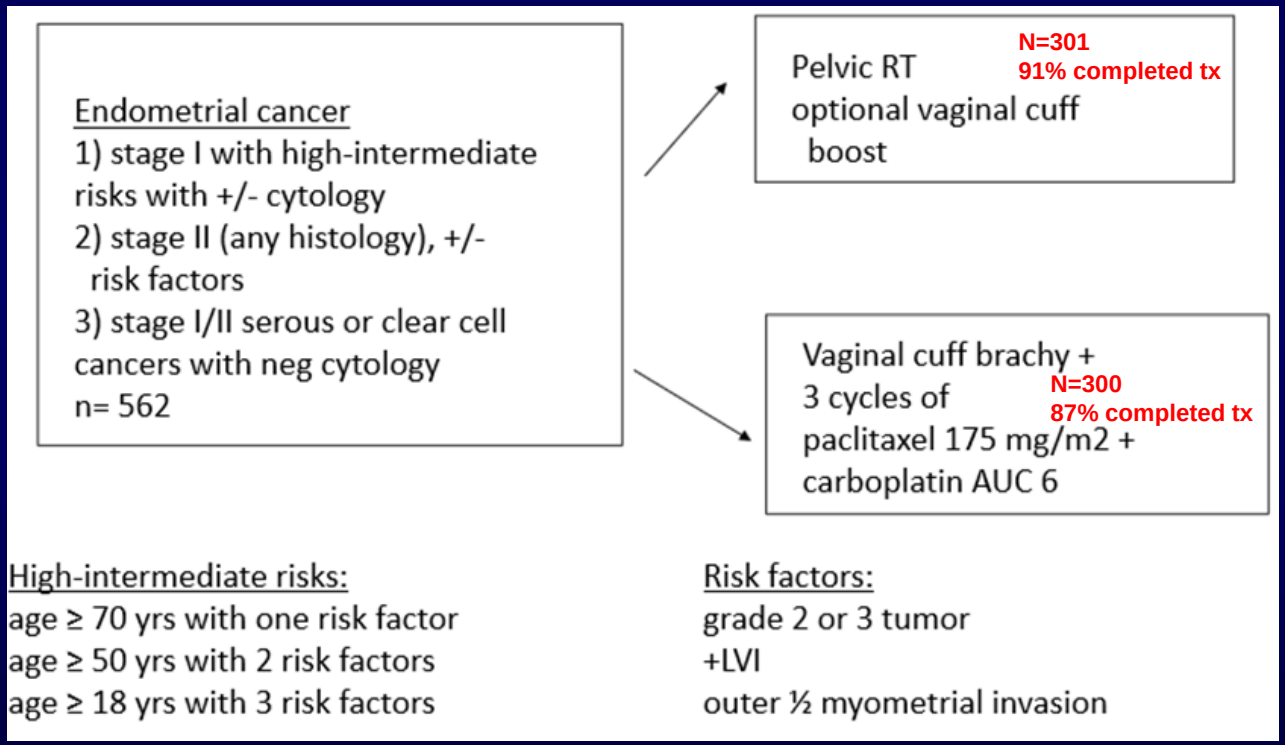
Fig 4. Survival by treatment and stage.

- Stage, residual disease, histology/grade, positive para-aortic node and cytology, pelvic metastases and age were significantly associated with RFS

Randall ME. JCO 2006

GOG-249

Primary objective: To determine if treatment with BRT and CT (VCB/C) reduces the rate of recurrence or death (RFS) compared to Pelvic RT (PXRT)



Secondary objectives: OS, patterns of failure, toxicity/functioning between arms

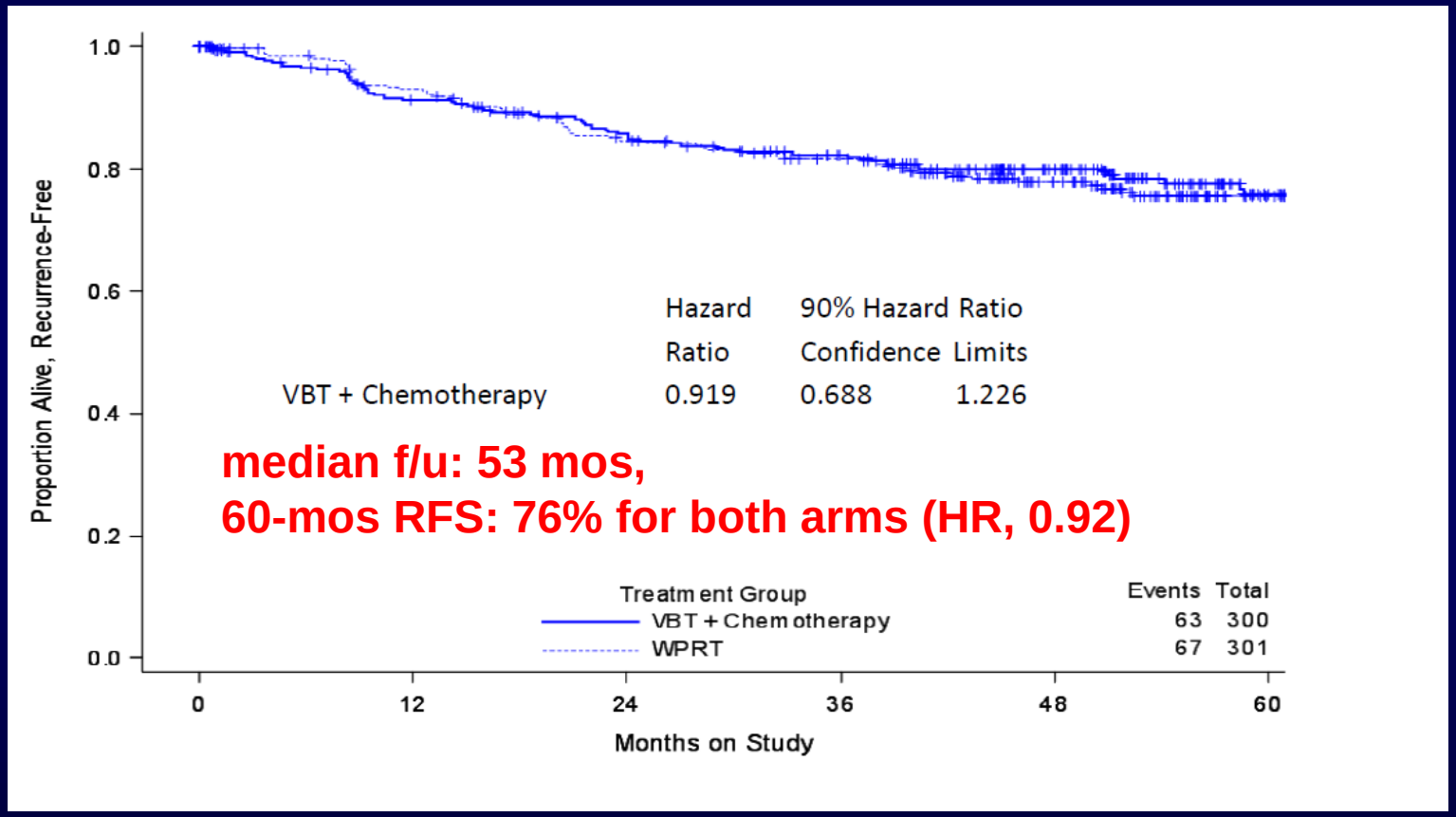
Randall ME. JCO 2019

GOG-249 (Characteristics)

	PXRT	VCB + Chemotherapy
Stage		
I	75.1	75.0
II	24.7	24.6
Histology		
Endometrioid		
G1	16.6	18.7
G2	36.2	34.3
G3	20.9	20.7
Serous	15.3	14.0
Clear Cell	5.0	4.3
Median Age	62 years	63 years

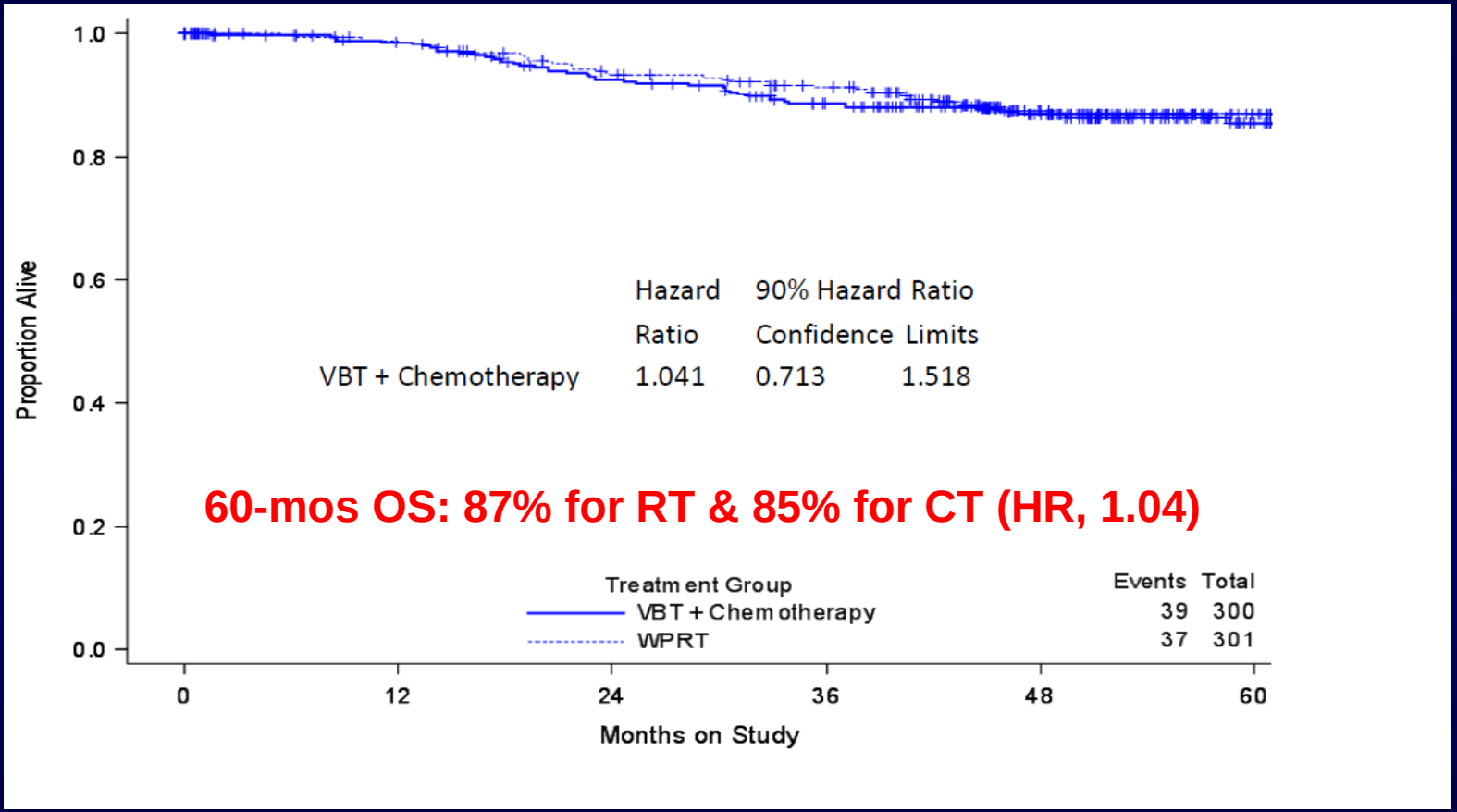
Randall ME. JCO 2019

GOG-249 (RFS)



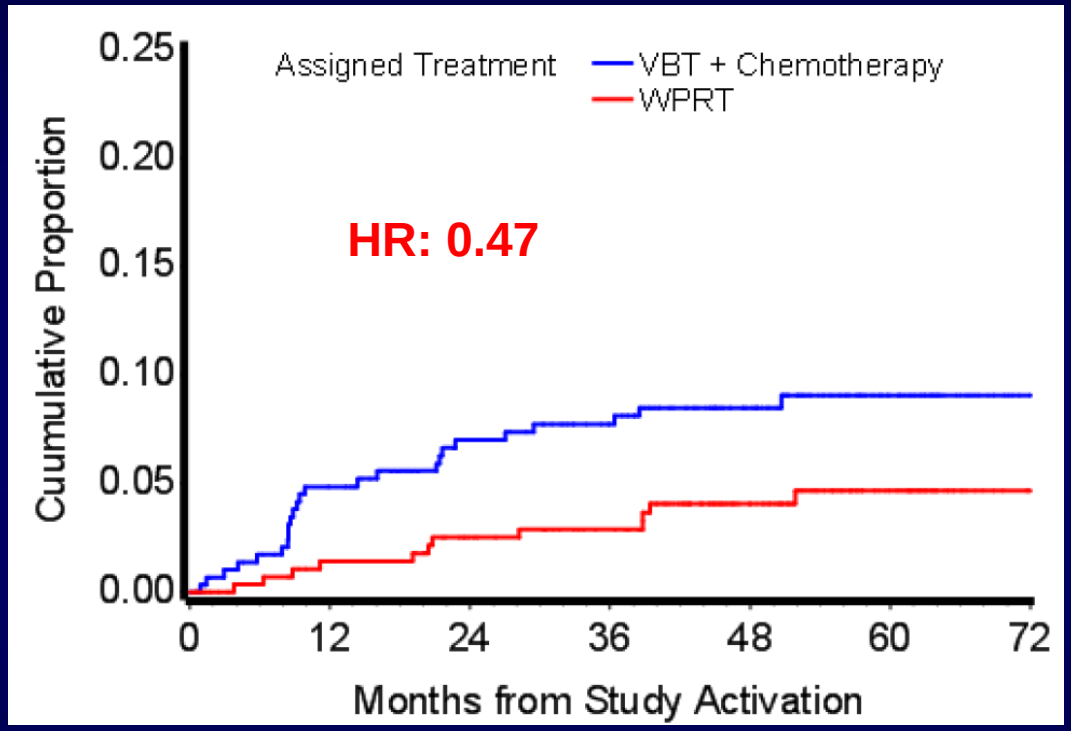
Randall ME. JCO 2019

GOG-249 (OS)



Randall ME. JCO 2019

GOG-249
(Cumulative incidence of pelvic/PA recurrence)



- **Pelvic/Para-aortic nodal failures more common in VCB/C arm (estimated 9% at 5 years, vs 4% in the PXRT arm)**

Randall ME. JCO 2019

GOG-249 (Conclusion)

- **This study did not demonstrate superiority of CT over RT in high risk, early stage EC:**
  - **This conclusion applies to all subgroups, including patients with serous and clear cell histology**
  - **Lower nodal failure rate in RT arm**
  - **Distant failure is the predominant failure pattern in both arms (18%)**
- **Acute toxicity was greater in CT arm, late toxicity was similar in both arms**
- **Pelvic RT remains an appropriate treatment for high risk, early stage EC**

Randall ME. JCO 2019

Treatment Modalities

Combination of CT & RT Compared with RT Alone

- **Because increased pelvic relapse has been reported and did not show differences in survival with chemotherapy alone, the combination of EBRT with chemotherapy has been explored in both retrospective and prospective trials:**
  - **GOG-34**
  - **Finnish Study**
  - **GOG-184**
  - **NSGO-9501/EORTC-55991/MANGO**
  - **PORTEC 3**

1. *Morrow CP. Gynecol Oncol 1991*
2. *Kuoppala T. Gynecol Oncol 2008*
3. *Homesley HD. Gynecol Oncol 2009*
4. *Hogberg T. Eur J Cancer 2010*
5. *De Boer SM. Lancet 2019*

Treatment Modalities

Combination of CT & RT Compared with RT Alone

	GOG 34[1]	Finnish Study[2]	GOG184[3]	NSGO9501[4]	PORTEC 3[5]
Population (Stage)	1-3	1A-B, G3 1C-3A	3-4	1-3	1-3
n	181	157	586	534	660
Regimen	RT RT→Doxo8	RT (split) CEP/RT/CEP/RT/CEP	RT→AP6 RT→TAP6	RT RT+CT	RT CTRT
PFS	-	NS	NS	69/78 HR 0.63*	69/76 HR 0.70*
OS	NS	NS	-	HR 0.69 (NS)	76/81 HR 0.70*

1. *Morrow CP. Gynecol Oncol 1991*
2. *Kuoppala T. Gynecol Oncol 2008*
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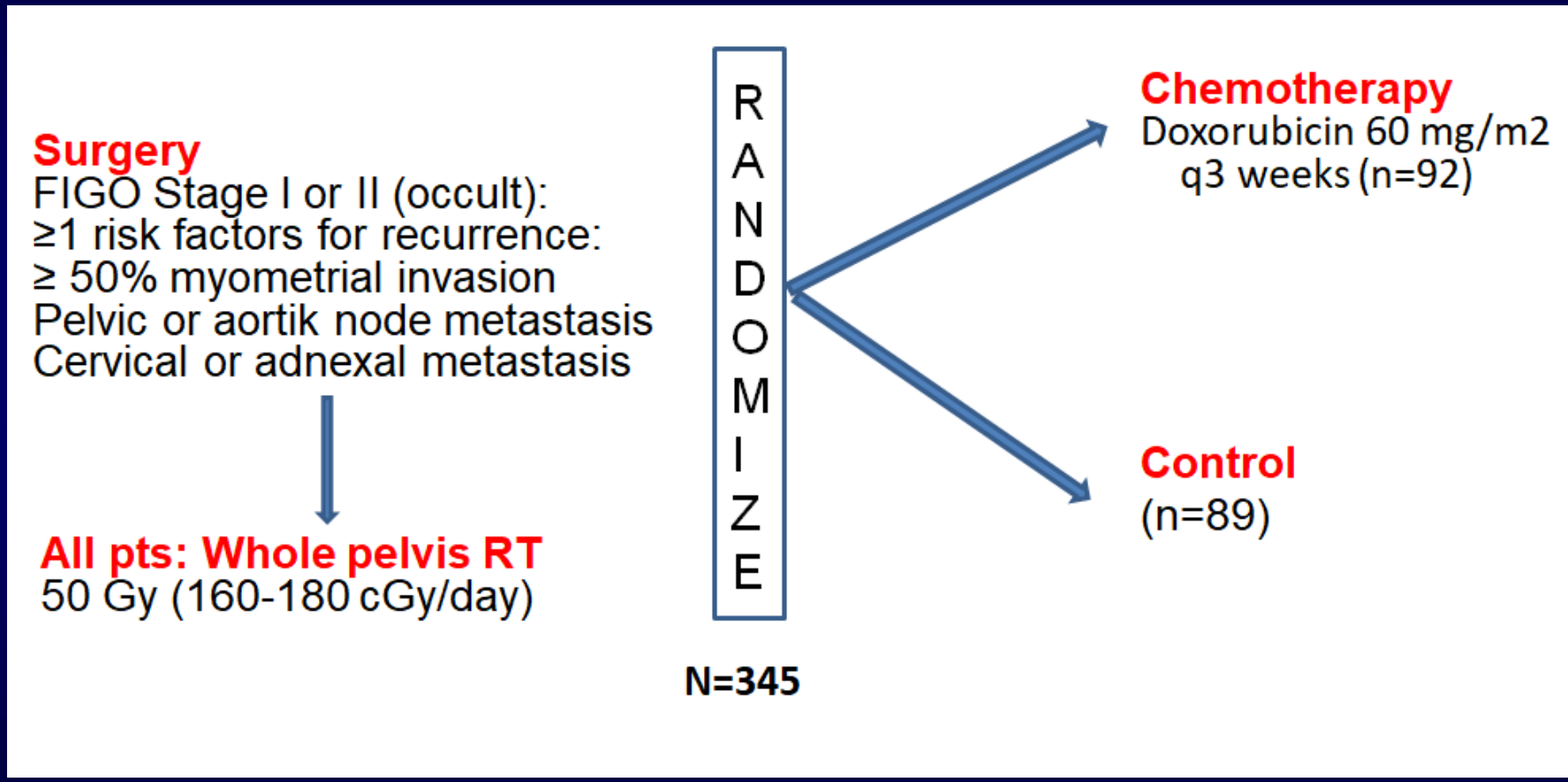
GOG 34



Morrow CP. Gynecol Oncol 1990

GOG 34

- No statistically significant difference in survival and RFI
- No significant difference in recurrence patterns
- Due to protocol violations, small sample size and substantial number of patients lost to f/u, the authors concluded that the trial failed to determine the effect of the addition of sequential doxorubicin

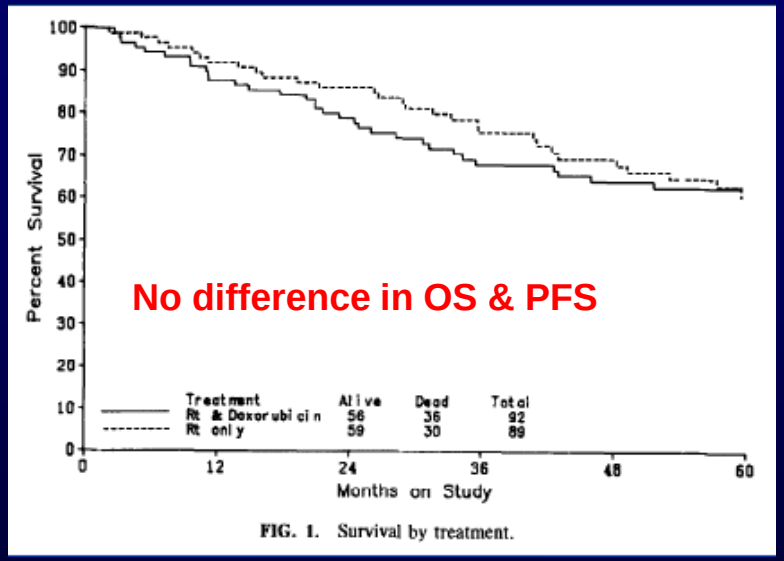


FIG. 1. Survival by treatment.

Morrow CP. Gynecol Oncol 1990

RTOG 9708 (Phase II)

Surgery
High risk EC
(grade 2-3 with ≥50% MI, cervical stromal invasion or pelvic confined extrauterine disease

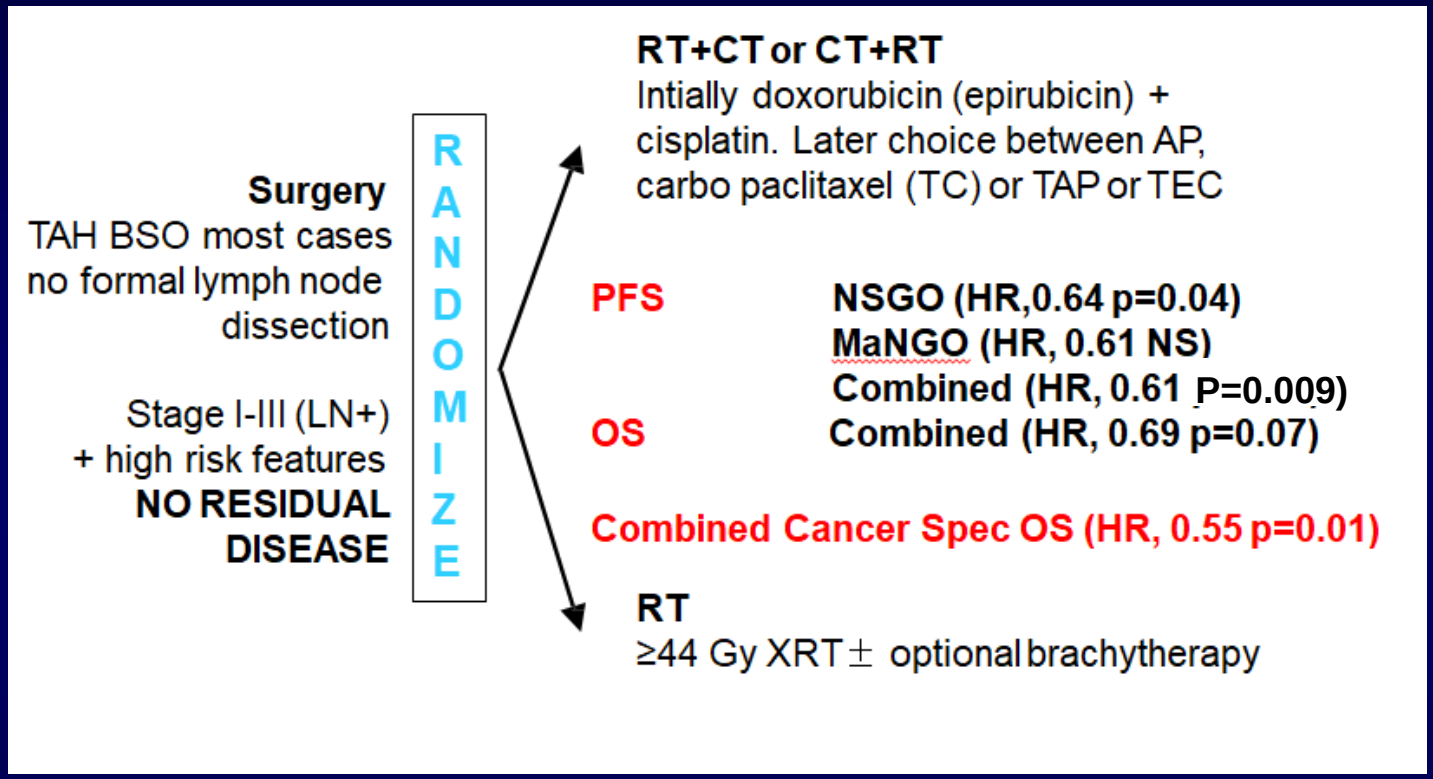
n=46 pts

Treatment
Cis 50 mg/m2 D1 & 28 during RT (45 Gy) to pelvis followed by BRT and then Cis 50 mg/m2 and Paclitaxel 175 mg/m2 X4 cycles q4 weeks

- **At 4 years: pelvic, regional and distant recurrence rates: 2%, 2% and 19%**
- **4 year OS and DFS 85% and 81%**
- **4 year OS and DFS for stage III pts: 77% and 72%**
- **No recurrences for stage IC-IIA**
- **Manageable toxicity**

Greven K. Gynecol Oncol 2006

NSGO EC-9501/EORTC-55991/MANGO



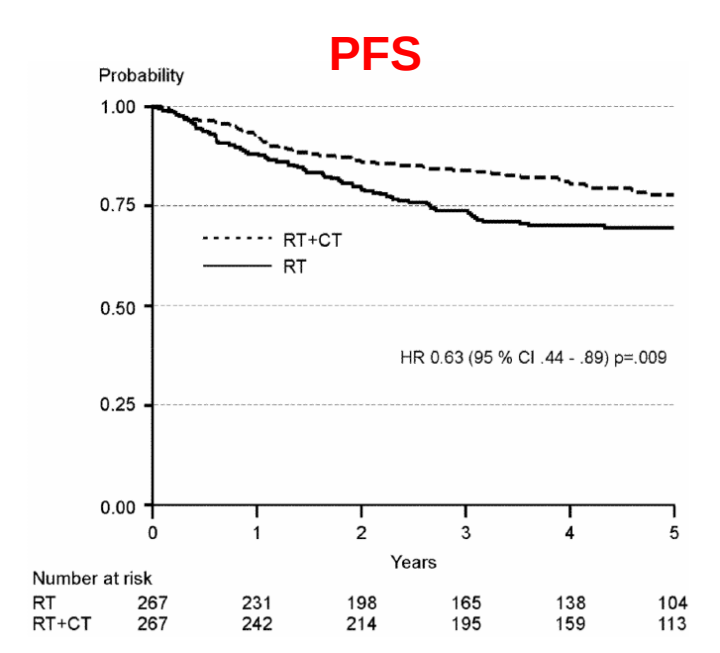
- **The pooled analysis of these two trials reported on a total cohort of 534 pts and showed improved PFS (HR 0.63; p=0.009) and a trend for improved OS (HR 0.69; p=0.07) with the addition of CT to EBRT**

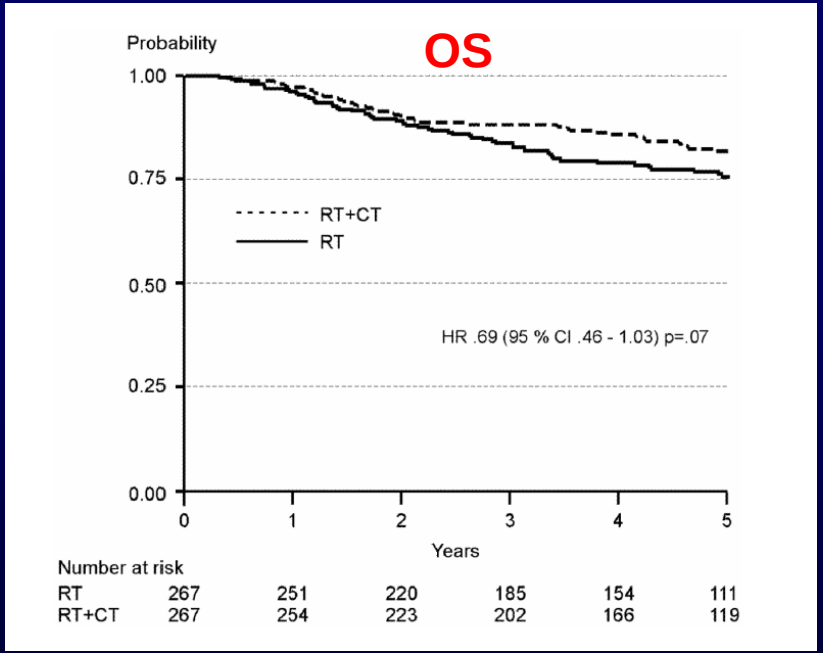
Hogberg T. Eur J Cancer 2010

NSGO EC-9501/EORTC-55991/MANGO

Pooled data failure-free survival (FFS) EC:

- With the addition of CT to EBRT:
  - #534 pts
  - Improved PFS (HR 0.63; p=0.009)
  - Trend for improved OS (HR 0.69; p=0.07)





Hogberg T. Eur J Cancer 2010

Meta-Analysis (Cochrane)

- **Randomised controlled trials comparing adjuvant chemotherapy with any other adjuvant treatment or no other treatment:**
  - **Five RCTs compared no additional treatment with additional chemotherapy after hysterectomy and radiotherapy**
  - **Four trials compared platinum based combination chemotherapy directly with radiotherapy**
- **Small benefit (4%) in PFS and OS after platin-based adjuvant CT, irrespective of RT**
- **RT reduced pelvic recurrence was underpowered**
- **CT was found to be less effective in reducing pelvic recurrence than RT**

Johnson N. The Cochrane database of systemic reviews 2011

Finnish Trial

- #156 pts:
  - EBRT alone or
  - EBRT given in a sandwich regimen with CEPX3
  - 66% Stage I, 66% Grade 1/2
- No OS difference (p=0.77)
- Recurrences: 18% (RT), 23% (CRT)
- More toxicity with CRT arm

Kuoppala T. Gynecol Oncol 2008

PORTEC 3 Trial

High-risk endometrial cancer

Endometrioid Gr 3 deep invasion or LVSI (or both)

Endometrioid-type stage II or III

Stage I to III serous or clear cell

41-45% III **23-26% S/CC**

- Uniform treatment schedule
- Upfront pathology review
- QoL analysis

RANDOMIZE

n=660

RT alone

48.6 Gy (#1.8 Gy)

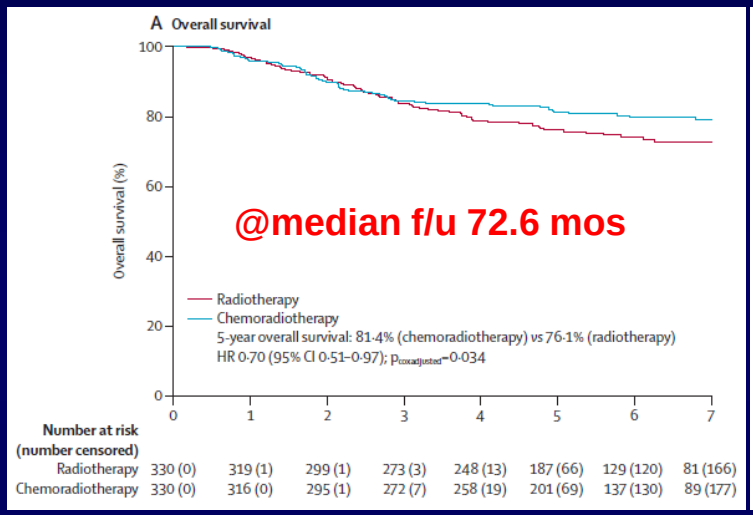
CTRT

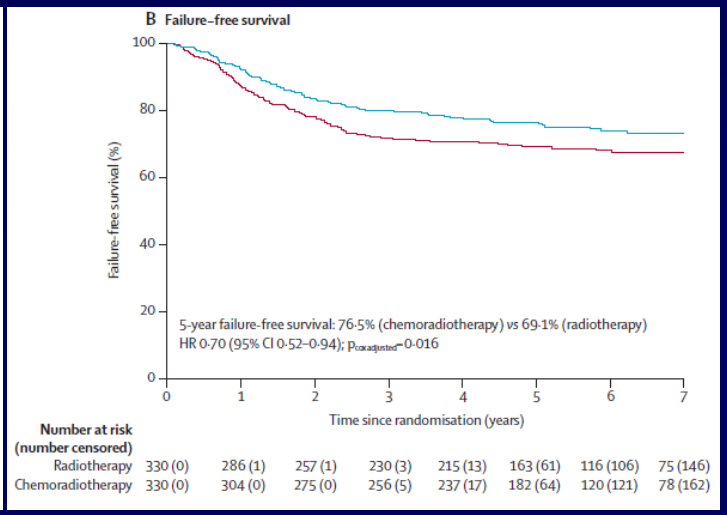
48.6 Gy (#1.8 Gy) cisplatin 50 mg/m² given during RT then #4 carboplatin AUC5 and paclitaxel 175 mg/m²

De Boer SM. Lancet 2019

PORTEC 3 Trial

Overall survival and failure-free survival curves-All pts



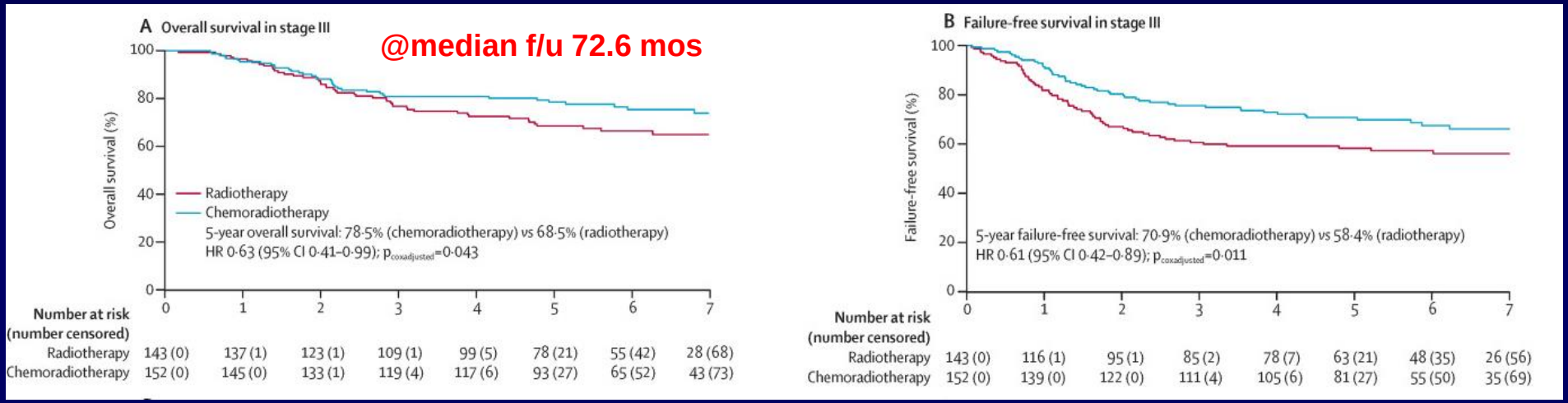


- **Updated analysis shows significantly improved OS & FFS with CTRT**
- **This treatment schedule should be discussed and recommended, especially for pts with stage III or serous cancers**

De Boer SM. Lancet 2019

PORTEC 3 Trial

OS & PFS Stage III EC

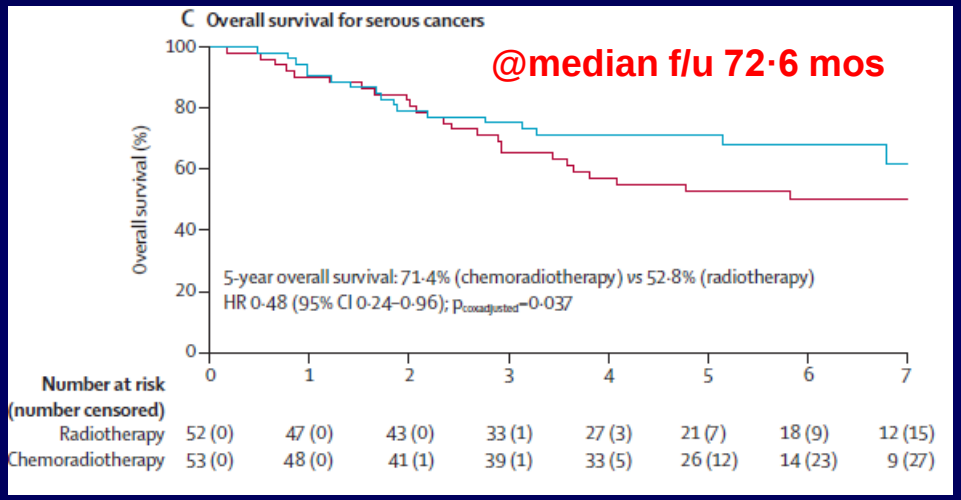


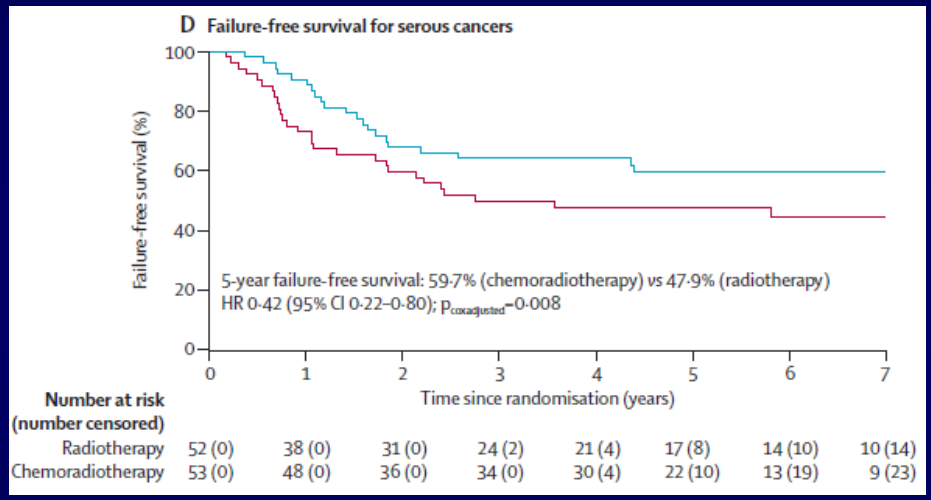
- **In a subgroup analysis: the largest FFS benefit with CTRT was observed in pts with stage III disease, have a baseline risk of recurrence than pts with stage I-II disease**
  - 5-yr OS 78.5% vs 68.5% (HR, 0.63; p=0.043)
  - 5-yr FFS 70.9% vs 58.4% (HR, 0.61 p=0.011)

De Boer SM. Lancet 2019

PORTEC 3 Trial

OS & FFS-Serous cancers





- **Significant improvements in OS & FFS were observed for serous cancers treated with CTRT versus RT alone:**
  - 5-yr OS: 71.4% vs 52.8% (HR, 0.48; p=0.037)
  - 5-yr FFS: 59.7% vs 47.9% (HR, 0.42; p=0.008)

De Boer SM. Lancet 2019

Treatment Modalities

Combination of CT & RT Compared with KT Alone

- **GOG-258 trial: To determine the added value of RT to CT alone in pts with stage III-IVA EC**

Matei D. NEJM 2019

GOG-258

Surgery: TAH/BSO, Pelvic and para-aortic lymph node sampling optional

ADJUVANT

96-98 % III Stage III or IVA EC
71-75% IIIC or Stage I-II
21 % Clear / UPSC

OS/PFS
QOL
Translational

*Ineligible Patients: Residual tumor after surgery > 2cm

RANDOMIZE

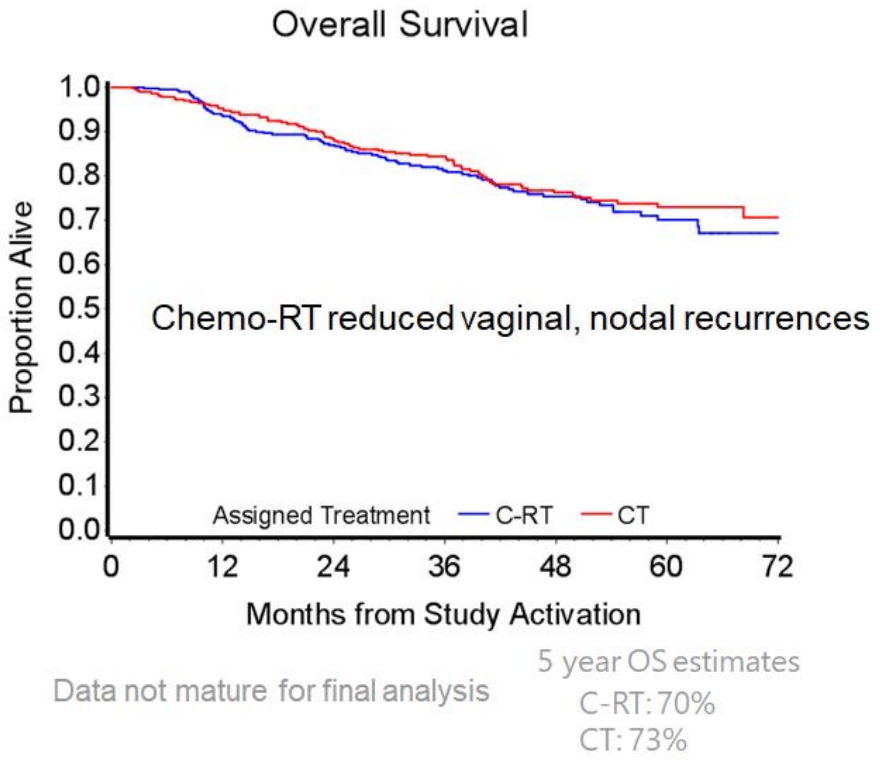
n=407
n=406

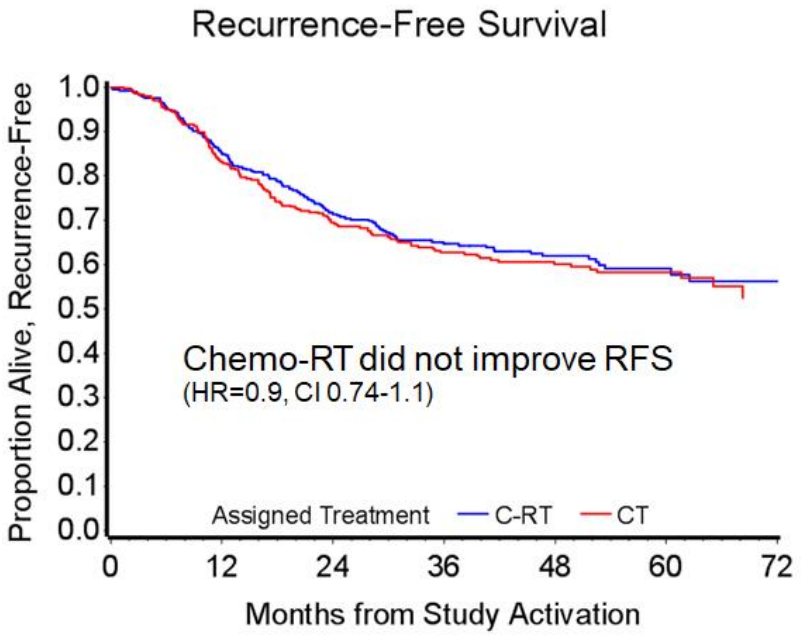
CTRT
Cisplatin 50 mg/m^2 D1,29
Vol.-directed 45G XRT + brachy
Followed by #4
Carboplatin AUC 5-6
Paclitaxel 175 mg/m2

CT
#6
Carboplatin AUC 6
Paclitaxel 175 mg/m^2

Matei D. NEJM 2019

GOG-258

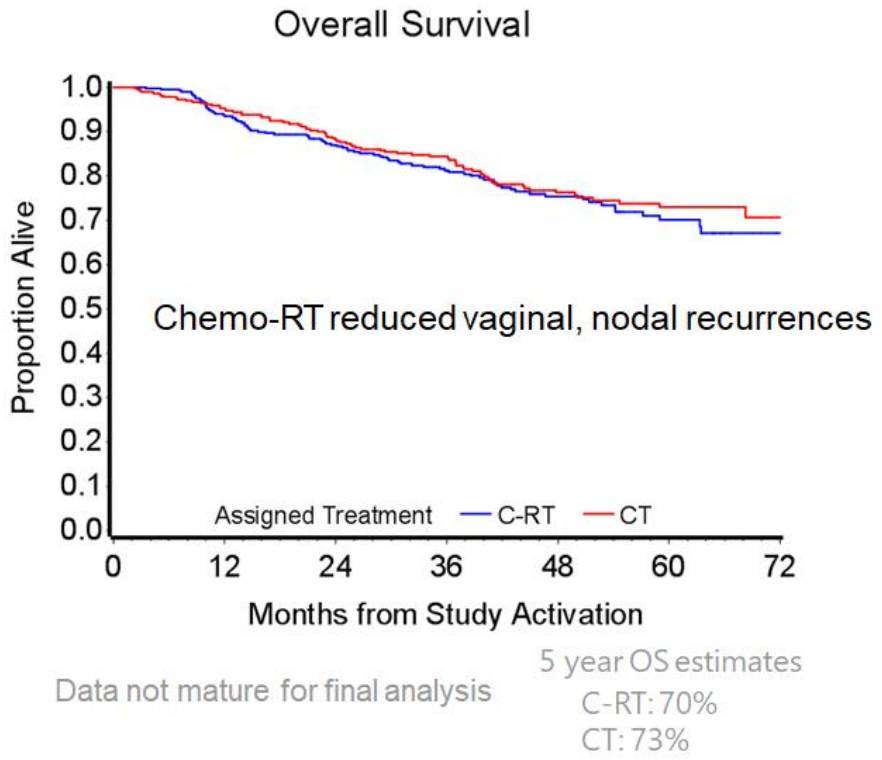


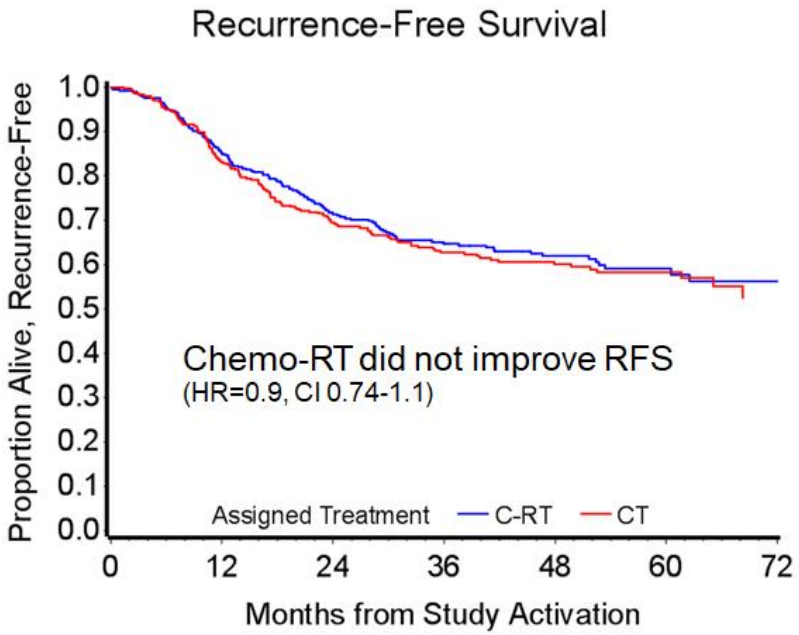


- **Median f/u: 47 mos**
- **At 60 months, the Kaplan–Meier estimate of the percentage of patients alive and relapse-free was 59% in the CTRT group and 58% in the CT-only**

Matei D. NEJM 2019

GOG-258



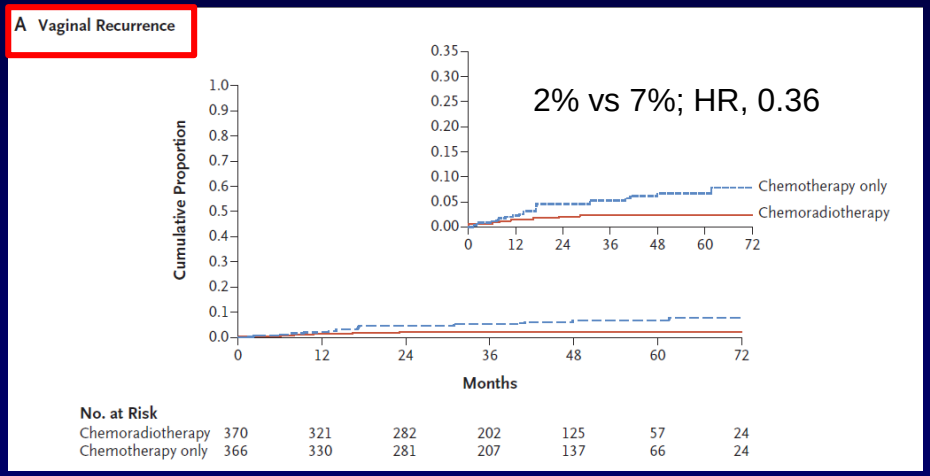


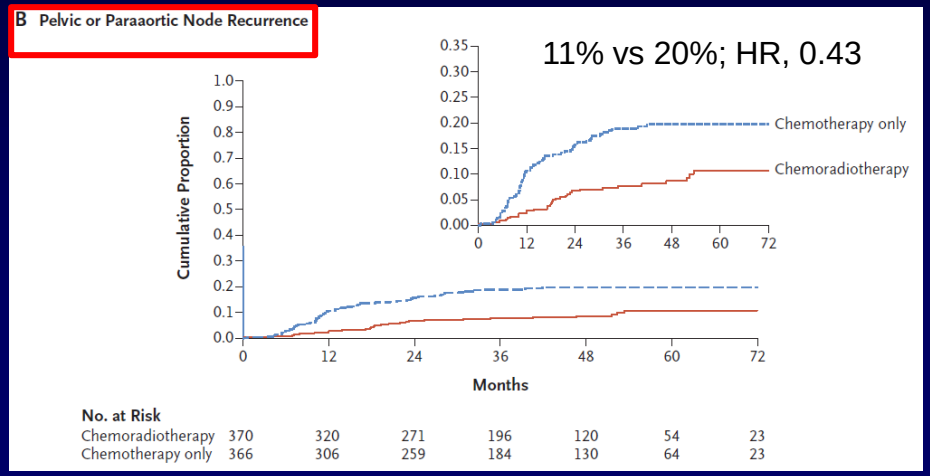
if we can get same result by using one therapy, there is no reason to use two?

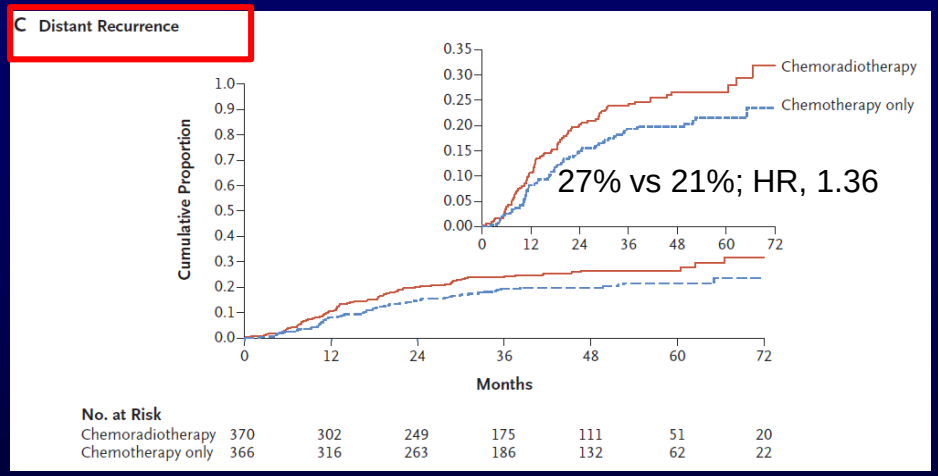
- **Median f/u: 47 mos**
- **At 60 months, the Kaplan–Meier estimate of the percentage of patients alive and relapse-free was 59% in the CTRT group and 58% in the CT-only**

Matei D. NEJM 2019

GOG-258



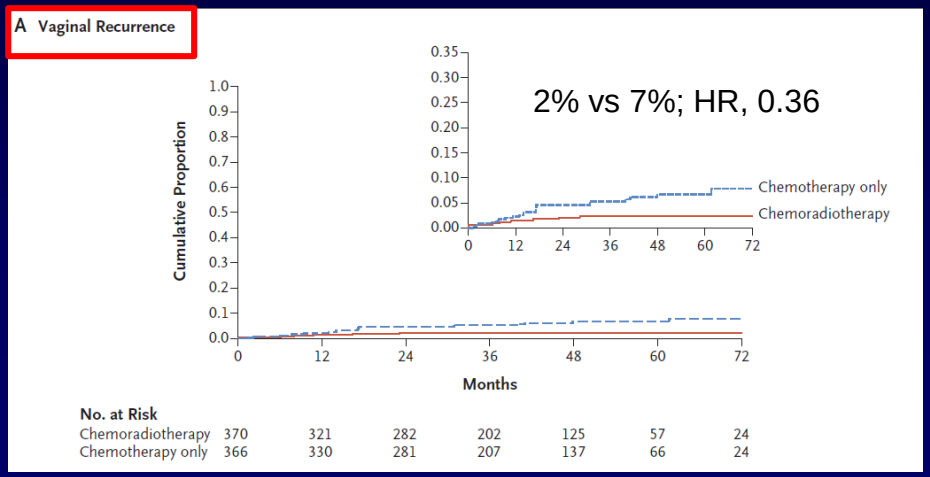


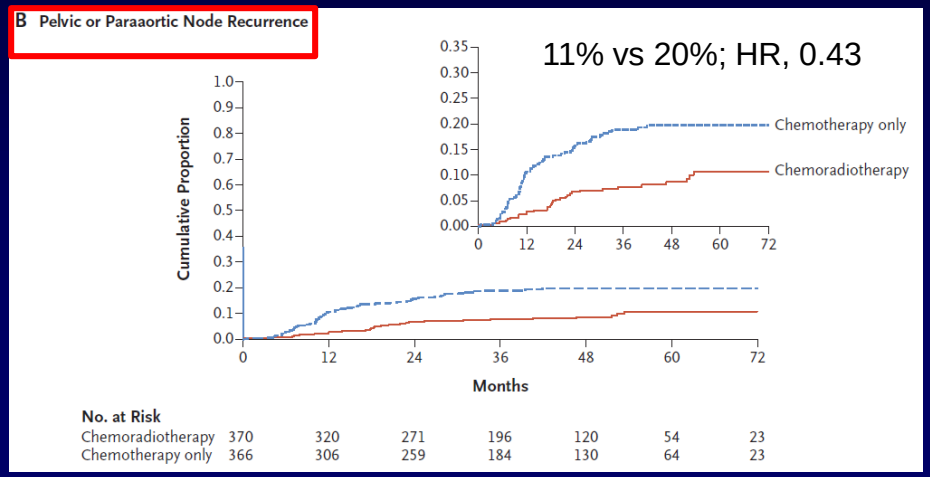


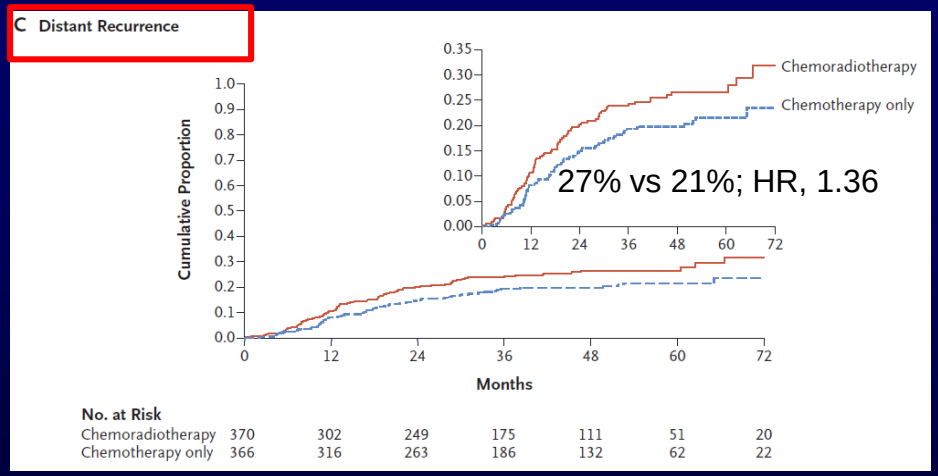
- **CTRT was associated with a lower 5-yr incidence of vaginal recurrence and PPLN recurrence than CT alone**
- **Distant recurrence was more common in association with CTRT**
- **Grade 3-5 AEs were reported in 58% in the CTRT arm and 63% in the CT arm**

Matei D. NEJM 2019

GOG-258







- **CTRT was associated with a lower 5-yr incidence of vaginal recurrence and PPLN recurrence than CT alone**
- **Distant recurrence was more common in association with CTRT**
- **Grade 3-5 AEs were reported in 58% in the CTRT arm and 63% in the CT arm**

***Physcians may consider addition for selected pts considered at very high risk for local recurrence**

Matei D. NEJM 2019

ESMO
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Q3: What are best evidence-based treatment strategies for the high-risk group, with/without nodal staging or LVSI and for endometrioid vs non-endometrioid cancers?

- Stage I endometrioid + gr 3 + ≥50% myometrial invasion, regardless of LVSI status
  - **Surgical nodal staging performed, node negative:**
    - Adjuvant EBRT with limited fields should be considered to decrease locoregional recurrence (LoE I, GoR B)
    - Adjuvant brachytherapy may be considered as alternative to decrease vaginal recurrence (LoE III, GoR B)
    - Adjuvant systemic therapy is under investigation (LoE II, GoR C)
      100% consensus
  - **No surgical nodal staging:**
    - Adjuvant EBRT is generally recommended for pelvic control and relapse free survival (LoE III, GoR B)
    - Sequential adjuvant chemotherapy may be considered to improve progression free and cancer specific survival (LoE II, GoR C)
    - There is more evidence to support giving chemotherapy and EBRT in combination rather than either treatment modality alone (LoE II, GoR B)
      100% consensus

ESMO-ESGO-ESTRO Concensus Conference Working Group, Ann Oncol 2016

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- Stage II endometrioid
  - Simple hysterectomy, surgical nodal staging performed, node negative:
    - Grade 1-2 LVSI negative: recommend vaginal brachytherapy to improve local control (LoE III, GoR B)
    - Grade 3 or unequivocal LVSI: recommend limited field external beam radiotherapy (LoE III, GoR B), consider brachytherapy boost (LoE IV, GoR C), chemotherapy is under investigation (LoE III, GoR C)
      1 abstain, 36 agree
  - Simple hysterectomy, no surgical nodal staging:
    - External beam radiotherapy is recommended (LoE III, GoR B), consider brachytherapy boost (LoE IV, GoR C)
    - Grade 3 or unequivocal LVSI: sequential adjuvant chemotherapy should be considered (LoE III, GoR B)
      100% consensus

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- Stage III endometrioid no residual disease
- Chemotherapy is recommended to improve PFS and CSS (LoE II, GoR B)
- EBRT is recommended to decrease pelvic recurrence (LoE I), with improvement in PFS (LoE I) and improvement in survival (Seer, Cochrane, Klopp, Secord) (LoE IV), GoR B
- There is more evidence to give chemotherapy and EBRT in combination than either alone in stage III (LoE III, GoR B)
  - IIIA: chemotherapy AND external beam radiotherapy to be considered
  - IIIB: chemotherapy AND external beam radiotherapy to be considered
  - IIIC1: chemotherapy AND external beam radiotherapy to be considered
  - IIIC2: chemotherapy AND extended field external beam radiotherapy to be considered

    2 abstain, 35 agree

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Q3: What are best evidence-based treatment strategies for the high-risk group, with/without nodal staging or LVSI and for endometrioid vs non-endometrioid cancers?

- Non endometrioid cancers (Serous, clear cell, carcinosarcoma, undifferentiated, mixed more than 10%) are regarded high risk (LoE III, GoR A).
- Serous and clear cell after comprehensive staging:
  - consider chemotherapy (LoE III, GoR B), clinical trials encouraged
  - Stage IA LVSI negative, consider vaginal brachytherapy only without chemotherapy (LoE IV,GoR C) (Barney)
  - Stage IB and higher, external beam radiotherapy may be considered in addition to chemotherapy, especially for node positive disease (LoE III, GoR C)
    100% consensus
- Carcinosarcoma and undifferentiated:
  - recommend chemotherapy (LoE II, GoR B) and consider external beam radiotherapy (LoE III, GoR C), clinical trials encouraged
    2 abstain, 35 agree

ESMO-ESGO-ESTRO Concensus Conference Working Group, Ann Oncol 2016

NCCN 2019
Histologic Grade/Adjuvant Treatment
Stage I

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
Endometrial Carcinoma

NCCN Guidelines Index
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Discussion

All staging in guideline is based on updated 2010 FIGO staging. (See ST-1)

CLINICAL FINDINGS — **HISTOLOGIC GRADE/ADJUVANT TREATMENT**[f,g,m,n]

Surgically staged: Stage I[d] →

FIGO Stage	Histologic Grade	Adjuvant Treatment
IA	G1, G2	Observation preferred or Vaginal brachytherapy if any risk factors[o,p]
	G3	Vaginal brachytherapy preferred or Consider observation if no myoinvasion and no lymphovascular space invasion[o]
IB[l]	G1, G2	Vaginal brachytherapy preferred or Consider observation if no risk factors[o]
	G3	RT (vaginal brachytherapy and/or EBRT) ± systemic therapy[q]

https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

NCCN 2019
Histologic Grade/Adjuvant Treatment
Stage II

National Comprehensive Cancer Network®

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CLINICAL FINDINGS — **HISTOLOGIC GRADE/ADJUVANT TREATMENT**[f,g,m,n]

Surgically staged:[d] **Stage II**[l,r] →

FIGO Stage	Histologic Grade	Adjuvant Treatment
II	G1, G2	Vaginal brachytherapy and/or EBRT[s]
	G3	EBRT ± vaginal brachytherapy ± systemic therapy (category 2B for systemic therapy)

See Surveillance (ENDO-9)

https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

NCCN 2019
Stage III, IV

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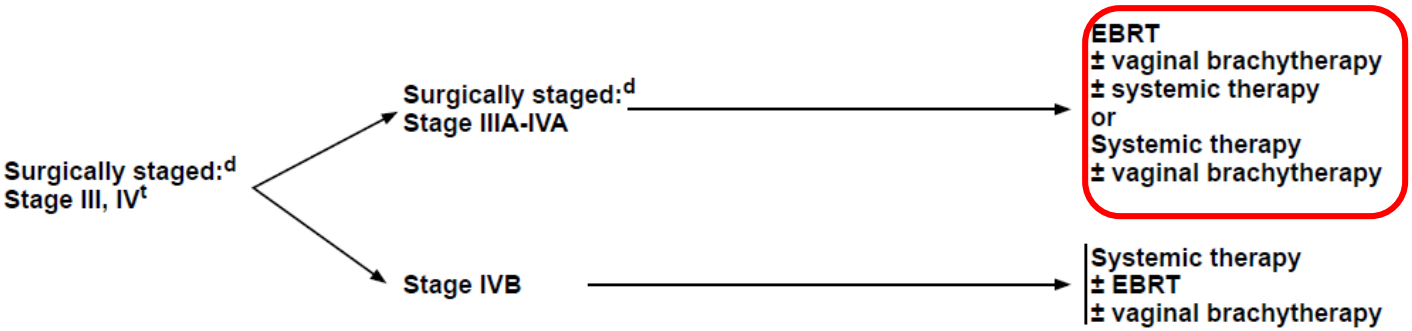
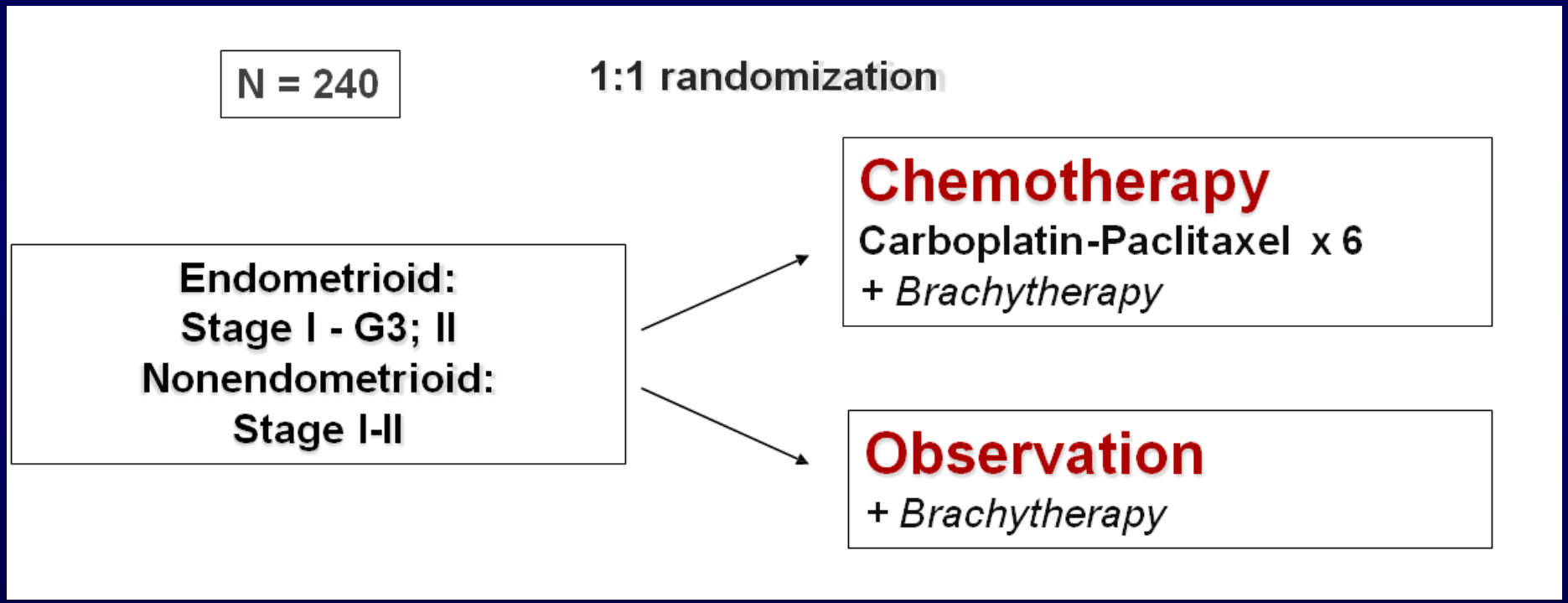
CLINICAL FINDINGS | **ADJUVANT TREATMENT[f,g,m]**



https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

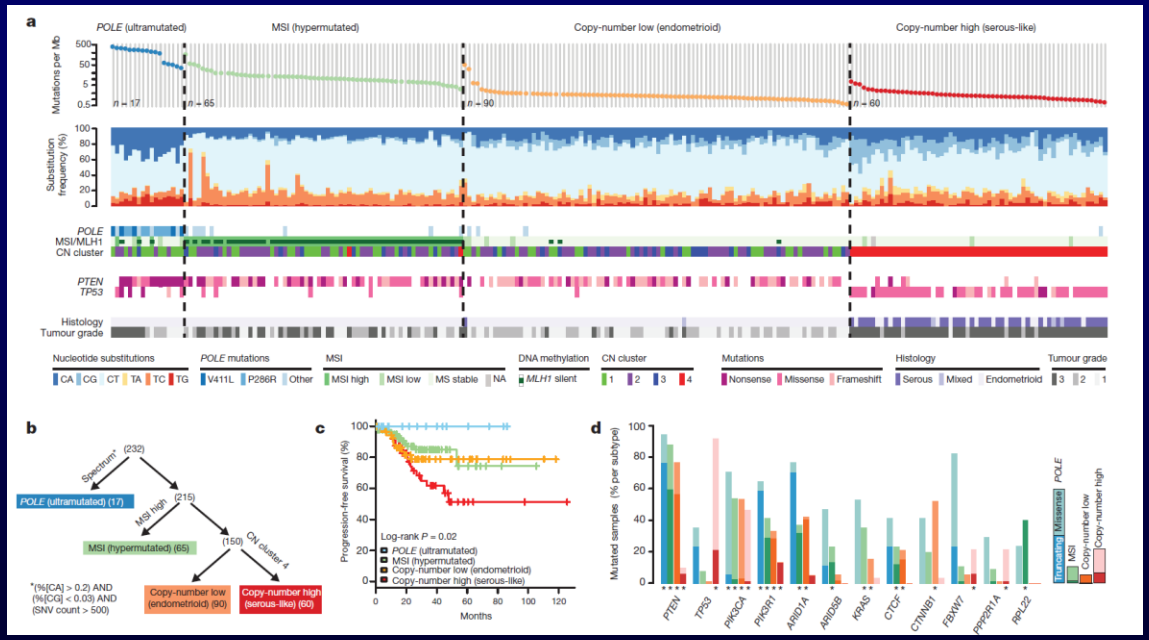
ENGOT-EN2-DGCG (*NCT01244789*) *(Phase II Ongoing)*



https://clinicaltrials.gov/ct2/show/NCT01244789

TCGA data

- Better understanding of the risk groups may improve clinical decision-making for HREC
- TCGA provided a molecular classification of EC with a clear correlation with PFS
- Integrated clinicopathological and molecular risk factors seems most effective to define risk, determine sensitivity to therapies



Conclusion

- Stage IB or II grade 3 endometrioid carcinoma may be treated with pelvic RT alone or with chemotherapy?
  - The answer will come with molecular profiling and identification of true HR pts
- Adjuvant CT is considered for pts with non-endometrioid cancers (bad histology group)
- Adjuvant chemotherapy is recommended for pts with stage III EC (with concurrent CT and RT?)
- Multidisciplinary treatment approaches to every individual patient is important to make a decision
- Translational research is essential to further individualise treatment

Selected References

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